

Regiochemical Effect of an α -Trimethylsilyl Group on Epoxide Reactions with Non-nucleophilic Bases

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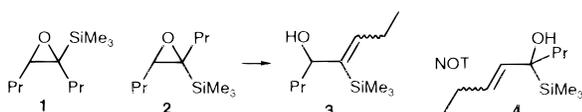
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Reactions of epoxides with strong, non-nucleophilic bases have been widely used for the synthesis of allylic alcohols.¹ Bases used to effect these rearrangements include R_2NLi ,^{1a,b} R_2NMgBr ,^{1a,c} diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP),^{1a,d} and *i*-Pr₂NLi/KO-*t*-Bu (LIDAKOR).^{1e} We report here that a silyl substituent can affect the regiochemical course of these rearrangements.

Ring opening reactions of α,β -epoxysilanes show a strong preference for cleavage of the C–O bond α to silicon by a wide variety of nucleophilic reagents, and a number of years ago, we introduced a synthesis of olefins and heteroatom-substituted olefins based on these reactions.² The reasons for this regiochemical preference are not well understood, although a number of possibilities have been suggested, including initial coordination of the nucleophile with both silicon and carbon and coordination with silicon followed by a 1,2-rearrangement.^{2d,3} In order to broaden our understanding of the regiochemistry of the reactions of α,β -epoxysilanes, we have studied the influence of an α -silyl group on the reactions of epoxides with non-nucleophilic bases, in which prior coordination with silicon would not be expected.

We have prepared epoxysilanes **1**, **2**, **7**, and **14** and have studied their reactions with Et₂NLi/Et₂O, *i*-Pr₂NLi/HMPA, R_2NMgBr /THF, LIDAKOR/THF, and (for **1** and **2**) DATMP. To the extent allylic alcohols are formed, the reactions are regioselective, and the allylic alcohols are those from α opening of the epoxide ring. The R_2NMgBr reagent gave allylic alcohols with all the epoxysilanes except **1**, which was unreactive. Et₂NLi was slower but did give an allylic alcohol from **7**. DATMP, which has been primarily used for acyclic and large ring epoxides, was the reagent of choice for epoxide **2**. The use of HMPA resulted in alternate reaction pathways with the epoxysilanes, as discussed below, and LIDAKOR did not give any major products cleanly with any of the epoxysilanes.



Treatment of epoxysilane **2** with DATMP^{4a} or with *c*-Hex(*i*-Pr)NMgBr^{4b} gave only the β -hydroxysilane **3**, from α

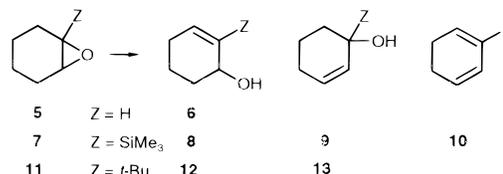
(1) (a) Crandall, J. K.; Appar, M. *Org. React.* **1983**, 29, 345–443. (b) Rickborn, B.; Thummel, R. P. *J. Org. Chem.* **1969**, 34, 3583–3586. (c) Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, 102, 1433–1435. (d) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, 96, 6513–6514. Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1705–1708. Marshall, J. A.; Audia, V. H. *J. Org. Chem.* **1987**, 52, 1106–1113. (e) Mordini, A.; Ben Rayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, 46, 2401–2410.

(2) (a) Hudrlik, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, 40, 2263–2264. (b) Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, 99, 1993–1996. (c) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *Tetrahedron Lett.* **1985**, 26, 139–142. (d) For review, see: Hudrlik, P. F.; Hudrlik, A. M. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 1–89.

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opening of the epoxide ring. From the DATMP reaction, **3** was isolated in 83% yield. It was distinguished from the alternate regioisomer, α -hydroxysilane **4**, by the NMR spectra.⁵ Epoxysilane **1** was less reactive than epoxysilane **2** to R_2NMgBr^{4c} (81% remained after 34 h) and to DATMP^{4d} (45% remained after 18 h), and no products were isolated.

Reactions of (trimethylsilyl)cyclohexene oxide (**7**) with Et₂NLi/Et₂O and with R_2NMgBr /THF gave mixtures of β -hydroxysilane **8**⁶ and diene **10**.⁷ The alternate regioisomer, α -hydroxysilane **9**,⁸ was present to the extent of only a few percent (identified by GC and GC/MS comparison). When **7** was treated with Et₂NLi/Et₂O, allylic alcohol **8** was the major initial product, but later diene **10** predominated.



Allylic alcohol **9** was *not* the precursor of diene **10**. When **9** was treated with Et₂NLi/Et₂O (room temperature (rt) for 10 min, then 42 °C), it was not converted to **10** (although reaction in the presence of an internal standard indicated that it very slowly disappeared, *e.g.*, 63% remained after 12 h). However, allylic alcohol **8** was converted to diene **10** under the reaction conditions.

Treatment of epoxysilane **7** with *i*-Pr₂NMgBr in THF/Et₂O or with *c*-Hex(*i*-Pr)NMgBr in THF produced allylic alcohol **8** and diene **10** in ratios more favorable to allylic alcohol **8**, with traces of α -hydroxysilane **9**. In a preparative experiment using *c*-Hex(*i*-Pr)NMgBr,^{4e} allylic alcohol **8** and diene **10** were obtained in 64% and 22% yields, respectively.

To gain insight on the effect of steric factors, we have studied reactions of 1-*tert*-butylcyclohexene oxide (**11**). Epoxide **11** yielded allylic alcohol **13**,⁹ the opposite regiochemistry to that found with silyl epoxide **7**. Treatment of **11** with Et₂NLi/Et₂O and with *c*-Hex(*i*-Pr)NMgBr/THF produced **13** in a slow reaction. Treatment of **11** with *i*-Pr₂NLi/HMPA (rt, 15 h) produced **13** in 80% yield. In the ¹H NMR spectrum of the crude product from the reaction with *c*-Hex(*i*-Pr)NMgBr,^{4f} the multiplets at δ 5.86 and 5.80 due to **13** were by far the major peaks in the olefin region; a small signal at δ 5.62 (crude triplet) suggests a maximum of 7% of regioisomer **12**.¹⁰

When (trimethylsilyl)cyclooctene oxide (**14**) was treated with *c*-Hex(*i*-Pr)NMgBr in THF, β -hydroxysilane **15** was formed in

(4) Reaction conditions: (a) DATMP/benzene/hexanes, 0 °C/4 h, rt/12 h. (b) *c*-Hex(*i*-Pr)NMgBr/THF, 0 °C/30 min, rt/20 min, then 40 °C/30 h. (c) *c*-Hex(*i*-Pr)NMgBr/THF, 0 °C/3 h, rt/10 h, then 45 °C. (d) DATMP/benzene/hexanes, 0 °C/2 h, then rt. (e) *c*-Hex(*i*-Pr)NMgBr/THF, 0 °C/2 h, rt/3 h, 55 °C/28 h. (f) *c*-Hex(*i*-Pr)NMgBr/THF, 0 °C/3.5 h, rt/12 h, 40 °C/92 h; product had a 1:1.5 ratio of **11**:**13** by GC.

(5) (a) Close examination of the ¹H NMR spectrum suggested the presence of two isomers (presumably **E** and **Z**) in an approximate ratio of 7:1. (b) Regioisomer **4** is not known, but a small multiplet about δ 5.3–5.4 in the ¹H NMR spectra of the crude products may have been due to about 2.5% (DATMP reaction) and <1% (R_2NMgBr reaction) of **4**.

(6) Fristad, W. E.; Bailey, T. R.; Paquette, L. A. *J. Org. Chem.* **1980**, 45, 3028–3037.

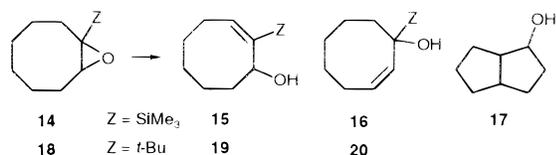
(7) Paquette, L. A.; Daniels, R. G.; Gletter, R. *Organometallics* **1984**, 3, 560–567.

(8) A comparison sample of **9** was prepared by treatment of cyclohexene with Al(SiMe₃)₃·Et₂O: Altnau, G.; Rösch, L.; Jas, G. *Tetrahedron Lett.* **1983**, 24, 45–46.

(9) The structure of allylic alcohol **13** was confirmed by comparison with the product from treatment of cyclohexenone with *tert*-butyllithium: (a) Still, W. C.; Mitra, A. *Tetrahedron Lett.* **1978**, 2659–2662. (b) Schumann, H.; Genthe, W.; Hahn, E.; Pickardt, J. *J. Organomet. Chem.* **1986**, 306, 215–225.

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a slow reaction. After 0 °C/3 h, rt/12 h, and then 43 °C/38 h, the product mixture contained 59% of **14** and 37% of **15** by GC. Chromatography gave a pure sample of **15**. The ¹H NMR



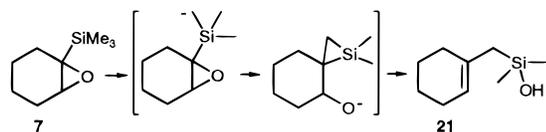
spectra of the crude sample showed that a triplet at δ 5.96 and a doublet of doublets at δ 4.9 were the only peaks in the vinyl region, indicating that α -hydroxysilane **16** was not present to any measurable extent.

Reactions of the *tert*-butyl analog **18** with base have been reported to yield isomeric allylic alcohols **19** and **20** in comparable amounts using Et₂NLi/PhH/reflux and using *t*-BuLi/pentane/reflux; in the former case, dienes were also formed.¹¹

The reactivity of the epoxysilanes to Et₂NLi/Et₂O was in some cases similar to that of their non-silyl analogs and in some cases lower. Epoxysilane **7** (which gave allylic alcohol **8**) had a similar reactivity to epoxide **5** (which gave **6**): when a mixture of **5** and **7** was treated with Et₂NLi/Et₂O/45 °C in the presence of an internal standard, both epoxides disappeared at similar rates. On the other hand, silyl epoxides **1**, **2**, and **14** gave slow reactions, with no major products observed. The corresponding non-silicon epoxides are known to react (4-octene epoxide → allylic alcohol; cyclooctene oxide → allylic alcohol + **17**).^{1a}

The use of HMPA resulted in different reaction pathways with the epoxysilanes. Reactions with lithium amide bases in solvents such as ether are believed to proceed *via* a base-epoxide complex and a *syn* β -elimination-type pathway.^{1a} HMPA is believed to break up the complex and has been found to facilitate the reactions and to affect the selectivity.^{1a,12,13}

With epoxysilanes **1**, **2**, and **14**, the use of HMPA resulted in desilylation; treatment of **14** with *i*-Pr₂NLi in HMPA (rt, 4 h) gave cyclooctene oxide in 81% yield. Treatment of epoxysilane **7** with *i*-Pr₂NLi/HMPA yielded the silanol **21** in 72% yield in a relatively fast reaction (<2 h at room temp). The



product can be rationalized by a pathway involving deprotonation of a methyl group on silicon followed by intramolecular epoxide opening.¹⁴ The disparate pathways taken in the reactions of epoxysilane **7** and the *tert*-butyl analog **11** (above) with *i*-Pr₂NLi in HMPA are most likely related to the stabilization of anions in the position α to silicon.

The order of reactivity of epoxysilanes **7** > **14** > **1** can be rationalized by ease of formation of the base-epoxide complex. The large amounts of diene (**10**) formed from reactions of **7** is unusual for this type of reaction (contrast **5** → **6**). The dehydration of **8** (but not **9**) to give diene **10** may involve allylic

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(12) Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541–1546.

(13) Morgan, K. M.; Gajewski, J. J. *J. Org. Chem.* **1996**, *61*, 820–821.

(14) A similar mechanistic pathway was recently suggested in reactions of 1,1-bis(trimethylsilyl)epoxides with *i*-Pr₂NLi/Et₂O to give silanols: Hodgson, D. M.; Comina, P. J. *Tetrahedron Lett.* **1996**, *37*, 5613–5614.

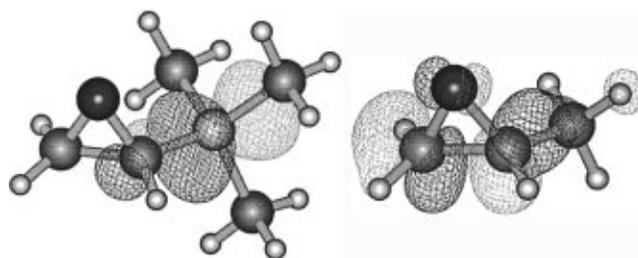


Figure 1. LUMO of **22** (left); LUMO of **24** (right).

Table 1. AM1 Coefficients

epoxide	$\Sigma c^2 \alpha\text{-C}$	$\Sigma c^2 \beta\text{-C}$	$\Sigma c^2 \text{Si or CR}_3$
7 (Me ₃ Si)	0.228	0.002	0.651
11 (<i>t</i> -Bu)	0.364	0.371	0.024
22 (Me ₃ Si)	0.232	0.002	0.648
23 (<i>t</i> -Bu)	0.400	0.415	0.037
24 (Me)	0.413	0.412	0.025

metalation, which would be facilitated by the stabilization of the allylic anion by silicon.

The regioselectivity of the reactions of epoxysilane **2** (to form **3**) can be rationalized by prior formation of the least hindered complex between the aluminum or magnesium amide and the epoxide oxygen.^{1a,d} However, the regiochemistry of the ring openings of epoxysilanes **7** and **14** is remarkable. Although the C–Si bond is longer than the C–C bond, the comparison of the reactions of **7** and **14** with those of the *tert*-butyl epoxides **11** and **18** is noteworthy. A conformational search^{15a} to examine the role of ground state conformational preferences for epoxides **7** and **11** yielded comparable results: a number of low-energy conformations of similar energy, the two expected chair conformations with different rotational conformers of the silyl and *tert*-butyl groups.

We believe the α opening of epoxysilanes with non-nucleophilic bases described here is related to the well-known nucleophilic α opening of epoxysilanes. We have found that the preference for α opening of epoxysilanes correlates with the character of the LUMO.¹⁵ For the epoxysilanes **7** and (trimethylsilyl)ethylene oxide (**22**), the AM1 LUMO isosurface is large at the Si and α carbon side of the molecule, and small at the β -carbon. For the alkyl-substituted epoxides **11**, *tert*-butylethylene oxide (**23**), and propylene oxide (**24**), the isosurface is large at both the epoxide carbons. A similar trend was found for *ab initio* calculations¹⁵ (HF/6-31G*) on silyl-ethylene oxide (**25**) and propylene oxide (**24**). The AM1 LUMO isosurfaces for (trimethylsilyl)ethylene oxide (**22**) and for propylene oxide (**24**) are shown in Figure 1, and the AM1 coefficients (Σc^2) are given in Table 1.

α,β -Epoxysilanes exhibit a regiochemical preference for α opening of the epoxide ring not only with nucleophiles, but with strong, non-nucleophilic bases as well.

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Supporting Information Available: Experimental details (8 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Calculations were carried out using HyperChem 4 and 5.01 with ChemPlus 1.5. (a) The conformational search was carried out using MM+, and the low-energy minima were refined using AM1.